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Title: Treatment for anxiety in paediatric Chronic Fatigue Syndrome (CFS/ME): A systematic review

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Abstract

Objectives: Anxiety is more prevalent in children with Chronic Fatigue Syndrome (CFS/ME) than in the general population. A systematic review was carried out to identify which treatment methods are most effective for anxiety in these individuals.

Setting: Systematic review

Participants: Studies were selected based on participant age (under 18) diagnosed with CFS/ME using CDC, NICE or Oxford criteria and a valid assessment of anxiety. The studies were also required to be observational or Randomised Controlled Trials (RCT). Papers were excluded if the participants had fatigue due to other causes.

Results: The review found 8 studies that met the inclusion criteria. None of the studies specifically targeted anxiety but six studies measured anxiety as a secondary outcome. Of the six studies, 5 used CBT-type approaches and found that anxiety improved with this approach. One study used a drug treatment compared to a placebo, which resulted in improvements in functioning and a reduction in anxiety in both arms, suggesting that anxiety may decrease over time in CFS/ME patients as functioning improves. However, there was no evidence about how anxiety impacts on recovery, and no studies stratified outcomes according to anxiety diagnostic status or severity.

Conclusion: It is uncertain the best treatment approaches for anxiety in paediatric CFS/ME patients. Further research is therefore required to answer this question.

Article summary

- This systematic review identified publications investigating the treatment of anxiety in children with CFS/ME.
- Screening and data extraction were carried out by two reviewers independently.
- Foreign articles were included and translators were recruited to assist where necessary.
- Unpublished material was not included.
- Formal quality assessment of the cohort studies was not undertaken.

Keywords

Chronic fatigue syndrome; CFS/ME; Anxiety; paediatric; child and adolescent psychiatry

Background

Chronic Fatigue Syndrome (CFS)/Myalgic Encephalomyelitis (ME) is a chronic condition of unknown aetiology consisting of disabling fatigue, malaise, difficulty sleeping, joint/muscle aches and difficulty concentrating[1]. The prevalence of CFS/ME in teenagers varies from 0.5%-2.4% depending on the diagnostic criteria and methodology used[2-4]. CFS/ME can have a very debilitating impact on children with one study showing a 40% or less school attendance rate in 62% of children with CFS/ME[5]. Children experience difficulty concentrating and impairments in cognitive function which have a significant impact on education[6].

Anxiety is a relatively common mental health condition; in the general population it is estimated that 5-19% of all children suffer from anxiety[7]. Children with CFS/ME experience higher rates of anxiety than the normal population, with one study showing rates of 38% in teenage girls[8]. Specifically, separation anxiety and social phobia were found to be the most prevalent subtypes of anxiety in paediatric CFS/ME[8]. Children with chronic illness might be more anxious as a reaction to being ill, a 'threatening environment' or other psychological factors as a result of their condition[9].

It is unclear whether children with CFS/ME develop anxiety as a result of their condition, whether psychological difficulties might pose a vulnerability to developing CFS/ME[2], or whether an external factor might increase the likelihood of an individual developing both anxiety and CFS/ME. Being diagnosed with CFS/ME has a severe impact on social life and attending school, which could potentially have a causative effect of depression and/or anxiety[10]. This may be compounded by the stigma surrounding CFS/ME and the inability to fully explain this illness[10, 11]. It is also possible that a biological mechanism is responsible for both the development of CFS/ME and anxiety, with some evidence of cortisol levels being implicated in CFS/ME in children and clear evidence of cortisol being linked to anxiety[12-14].

Anxiety may have a negative impact on recovery in paediatric CFS/ME by affecting an individual's ability to follow the evidence-based treatment for CFS/ME, which includes gradually increasing their activity levels. For example, in children, the aim of treatment for CFS/ME would be to gradually increase school attendance; however anxiety about going to school may prevent them from doing this. Therefore, co-morbid anxiety may need a specific treatment target in paediatric CFS/ME. The aims of this review are to establish what is known about treatment approaches for anxiety in children with CFS/ME and what is known about the impact of co-morbid anxiety on outcome in CFS/ME. The aims of this review were to understand what the existing quantitative and qualitative literature tell us about current or previous treatment approaches for anxiety in children with CFS/ME including: what the outcome is for children with CFS/ME who are anxious compared to children who are not anxious; whether the outcomes for children with CFS/ME and co-morbid anxiety vary between studies and whether particular treatment approaches have different outcomes.

Methods

Data sources and search strategy

The search strategy for this systematic review incorporated the use of the Cochrane library and OVID to search the databases MEDLINE, EMBASE and psychINFO. It was designed to identify longitudinal studies (randomised trials and cohort studies), which included children with diagnosed CFS/ME and a measure of anxiety, to address the review questions. An information specialist was consulted about search strategy, resulting in a final list of search terms using Medical Subject Headings and free text (see supplementary material). Limits were applied according to the inclusion criteria. Final searches were conducted in July 2016.

Study selection (inclusion and exclusion criteria)

Initial screening was by title and abstract to assess eligibility (N = 162). From this stage onwards two reviewers (SS, ML) independently assessed each paper at each stage. Conflicts were resolved by discussion, with reference to the review protocol. Following the initial screening stage, we screened full texts of the articles (N = 46) to ascertain whether they met all the eligibility criteria.

Reference lists of all included articles were also hand searched. In addition, all published systematic reviews post 2010 on interventions in paediatric CFS/ME were searched and one article by Knight et al (2013) was found[15]. The reference list of this article was then searched for studies conducting interventions in paediatric CFS/ME that met the eligibility criteria for this review. One reviewer (ML) conducted this stage and five articles were found to meet the inclusion criteria.

Limits were applied to filter articles predominantly for children under age 18 as this was part of the inclusion criteria in addition to studies including and after the year 1991 as this is when CFS/ME was first classified as a diagnosis. Study participants were required to have a diagnosis of CFS/ME diagnosed according to Centre for Disease Control and prevention (CDC) criteria[16], NICE (2007)[1] or Oxford criteria[17].We excluded studies with children who had an alternative reason for their fatigue.

We included both observational and clinical trials (randomised or quasi-randomised) of children with CFS/ME with a valid assessment of anxiety at baseline (including obsessive compulsive disorder, panic, phobia, generalised anxiety disorder, separation anxiety disorder, social anxiety disorder). A change in anxiety or fatigue on psychometrically validated assessments was required.

Foreign studies were also considered for inclusion with the help of native speakers to assist in translation and to determine whether the studies met the inclusion criteria. One foreign paper (Spanish) was included in this review, and a further one was considered but rejected at full text review (Dutch).

Data extraction

For all included articles, data was extracted using a data extraction form, collecting information such as the CFS/ME definition used, treatment/interventions provided, definition of response, details of the setting of the study, how children were recruited for the study, date of the study and child characteristics (including age). Two reviewers (SS, ML) independently carried out this process.

Data synthesis

There was insufficient comparable data to undertake a meta-analysis. Therefore, a narrative synthesis was undertaken.

Results

Identification of studies

A total of 250 records were found by database searching, and after duplicates were removed, 162 remained (figure 1). 46 articles were reviewed in full. Exclusion criteria were applied and 3 studies from the database search were found to meet the inclusion criteria for the review. An additional 5 studies were included found by hand searching the reference lists of articles reviewing interventions in paediatric CFS/ME published since 2010, resulting in 8 articles to be included overall.

Patient and study characteristics

Of the 8 articles, 5 were observational studies and 3 were RCTs. Anxiety was measured using self-report questionnaires including the Hospital Anxiety and Depression Scale (HADS)[21], the State-Trait Anxiety Inventory for Children (STAIC)[22], Spence Children's Anxiety Scale (SCAS)[23], and the Multidimensional Anxiety Scale for Children (MASC)[24]. 1 study used a diagnostic interview, the Development And Well-Being Assessment (DAWBA)[25] (table 1).

Sample sizes ranged from 1 to 135 (table 1) and ages ranged from 11-19 years. Most studies diagnosed participants according to the CDC criteria[16]. The majority of participants were female in all of the studies. One study found 15 years to be the average age of diagnosis in children with the prevalence of CFS/ME in this age group as 11 per 100,000 and a female to male ratio of 5:1[26]. Therefore, the samples in these studies do appear to be representative of the adolescent population.

Table 1. Summary of methodology and study design of included studies

Authors (year)	Country	Design	Number of participants	Mean age - years (SD)	CFS/ME Diagnostic Criteria Applied	Measure of Anxiety	Intervention	Treatment specifically targeted at or adapted for anxiety?	Outcome stratified by anxious versus non-anxious?	Length of follow-up
Chalder, et al (2002)	UK	Observational (outpatient treatment)	23 (18 at follow-up)	(range 11-18, median 15)	Sharpe et al (1991)	HADS anxiety Fear questionnaire	CBT based rehabilitation programme. Up to 15 sessions, 1 hour in duration.	No	No	6m
Diaz-Caneja et al (2007)	Spain	Observational (outpatient treatment) case study	1	15	Sharpe et al (1991)	MASC	CBT + fluoxetine (initially 10mg daily, increased after 1 week to 20 mg)	No	N/A	3m
Lloyd, et al (2012)	UK	Observational (outpatient treatment)	63 (52 at follow-up)	(Median 15)	Sharpe et al (1991)	SCAS	CBT via telephone based guided self-help – 6 fortnightly sessions, 30mins duration	No	No	6m
Nijhof et al (2012); Nijhof et al (2013)	Netherla-nds	Randomised control trial comparing internet-delivered CBT to usual care	135 (112 at long term follow-up)	Intervention group 15.9 (1.3) Control group 15.8 (1.3)	Fukuda et al (1994)	STAIC	Intervention: Internet delivered CBT consisting of psychoeducation and 21 modules, with parallel child and parent sessions. FITNET therapist individually tailored intervention and initially responded to emails weekly, decreasing to fortnightly. Mean treatment duration 26.2 weeks (SD 7.3). Control group: Treatment as usual including CBT (66%), rehabilitation treatment (22%), physical treatment (mostly graded exercise therapy; (49%), or alternative treatment (24%).	No	No	2.5 years
Rimes, et al (2007)	UK	Observational (prospective, community)	1 case of CFS at Time 1; 4 cases CFS at identified at Time 2	(Range 11-15)	Fukuda et al (1994)	DAWBA (interview)	None	N/A	N/A	4-6m
Rowe (1997)	Australia	Randomised control trial comparing drug treatment to placebo	71 (70 at follow-up)	Intervention group 15.3 (2.0) Control group 15.6 (2.0)	Fukuda et al (1994)	SSTAQ	Intervention: 3 monthly infusions of gammaglobulin. Control: 3 monthly infusions of a dummy solution. Both arms received information on Visiting Teacher Service, Distance Education, and availability of Social Security support and had access to a support group.	No	No	6m

Van de Putte, et al (2007)	Netherlands	Observational (prospective, community)	40 at baseline (36 at follow-up)	16.0 (1.5)	Fukuda et al (1994)	SSTAQ	None	No	No	18m
Wright et al (2005)	UK	Randomised control trial comparing Stairway to Health Intervention to Pacing	13 (11 at follow-up)	Intervention group (range 12-16.9) Control group (range 8.9-16.9)	Sharpe et al (1991)	HADS anxiety	Intervention: STAIRway to Health intervention is a structured rehabilitation programme including conceptualising CFS as having both physical and psychological components, formulating and addressing vicious cycles around activity, sleep, social isolation, physical deconditioning, and developing adaptive coping strategies whilst challenging negative and unhelpful attributions about illness and the future. Control: Pacing focuses on limiting activity to the changing needs and responses of the body by avoiding overexertion and managing energy within an overall limit.	No	No	1y

CBT = Cognitive Behaviour Therapy; CIS-20 = Checklist of Individual Strength; CFS = Chalder Fatigue Scale; DAWBA = Development and Well-being Assessment; HADS = Hospital Anxiety and Depression Scale; MASC = Multidimensional Anxiety Scale for Children; SCAS = Spence Children's Anxiety Scale; SSTAQ = Spielberger State Trait Anxiety Questionnaire; STAIC = State-trait anxiety inventory for children

Treatment in anxiety for children with CFS/ME

No studies specifically targeted anxiety in children with CFS/ME. Out of the eight studies included, six employed an intervention aimed at remediating fatigue with anxiety being a secondary outcome measure[6, 27-32]. Two of the eight included studies were prospective studies that did not test an intervention. Rimes et al looked at factors such as anxiety predicting the development of CFS/ME and Van de Putte et al observed the prevalence of Alexythmia in CFS/ME patients and assessed anxiety as a possible confounder[2, 33]. Therefore these studies were unable to inform us about the treatment of anxiety for children with CFS/ME. Of the treatment studies, four used CBT principles, one used a behaviour approach and one used an immunoglobulin (antibody), specifically IgG, drug treatment. The duration of CBT across the studies ranged from six 30 minute telephone sessions at fortnightly intervals[30], to twenty-one internet session modules over 26 weeks[6, 27, 34].

Wright et al's behavioural approach study was an RCT comparing two treatment approaches, one called 'pacing' and the other 'STAIRway to health'. Thirteen children were randomised into either group with stratification for age, sex and mobility. The 'pacing' arm involved exercising to the child's limits whilst adapting to an individual's bodily needs. The 'STAIRway to health' arm was a structured tailored incremental rehabilitation programme that took a more holistic approach to CFS/ME aiming to treat both physical and psychological symptoms including nutrition, sleep, social activities and emotional issues[32]. The clinic appointments were weekly for one month, twice weekly for the next three months, three times a week for the following 2 months and four times weekly for the remaining 6 months. STAIRway had a greater emphasis on coping strategies to deal with both the physical and psychological implications of CFS/ME and showed a greater improvement in anxiety levels[32].

In the four studies taking a CBT-type approach, anxiety improved with treatment (table 2), which suggests that cognitive behavioural treatment for CFS/ME may improve anxiety. In the study by Chalder et al, 23 participants were offered family based CBT. There was a significant improvement in anxiety related outcomes as a result of this approach[28]. It involved 15 fortnightly hourly sessions using a graded therapy method including a sleep routine and was implemented by patients and family with therapist guidance. The goal in this study was for children to return to full time education. Activity goals were set to include tasks such as walking, school work and attending social events. The activities were slowly increased and the aim to disassociating symptom relief with activity cessation. A sleep routine was also established in addition to changing perceptions of their illness to prevent negative thoughts[28].

Table 2. Details of components in provided in CBT interventions

Study	Intervention	Duration and frequency
Chalder et al[28]	CBT-based rehabilitation programme including graded approach to increasing activity and establishing a sleep routine. Cognitive work was included where necessary.	Up to 15 hourly sessions, face-to-face.
Diaz-Caneja et al[29]	CBT (no further details given) + fluoxetine (initially 10mg daily, increased after 1 week to 20 mg).	No details given.
Lloyd et al[30]	CBT which addressed unhelpful beliefs including fears about symptoms/activity. Activity diaries were used to establish a consistent routine and achieve a balance between activity and rest. The programme emphasised gradually increasing activities, including school, home, socialising and exercise, and establishing a regular sleep routine. Social and emotional problems addressed if time allowed.	Up to 6 x 30 minute sessions, by telephone, based on self-help manual.
Nijhof et al[27, 34]	CBT in the FITNET program consisted of two sections, a psycho educational section and cognitive behavioural therapy section. Parents had parallel modules.	21 interactive modules delivered via the internet, with e-consultations from therapists.
Wright et al[32]	Structured Tailored Incremental Rehabilitation (STAIRway) programme - appears to be a CBT based intervention. Sessions were spent developing a holistic understanding of CFS, formulating the vicious cycles that exacerbate fatigue, including nutrition, sleep patterns, physical deconditioning, social isolation, school nonattendance, and emotional cycles. Adaptive coping strategies were developed, and negative attributions about illness and the future addressed. This was in addition to pacing activity to the changing needs and responses of the body by exercising to the point of tolerance, and avoiding overexertion.	Approximately 18 sessions over 1 year, beginning weekly and then gradually spacing out more. Face-to-face.

Diaz-Caneja et al reported a moderate response to combined CBT and fluoxetine treatment in a single case study[29]. They found that with this approach there was increased tolerance to activity although the subject still felt tired. However, the specific components of treatment are not clear and treatment appears to have been ongoing at the time of writing the case study.

Lloyd et al trialed a telephone self-help intervention involving 63 participants undergoing 6 fortnightly 30 minute sessions based on a CBT model that also showed a significant improvement in anxiety levels[30]. This approach addressed any fears the participants had towards the programme in addition to completing activity diaries and developing a better sleep routine. Fatigue and school attendance were the primary outcomes, with anxiety being a secondary outcome measure.

Nijhof et al's RCT compared internet-based CBT to traditional methods in 135 participants. The internet-based CBT, FITNET, consists of a psyco-educational part for patients and parents in addition to CBT based on that developed by the Expert Centre for Chronic Fatigue[27, 35]. Patients were able to send emails and therapists replied to 'e-consults' on the same day each week or depending the treatment plan. The study found a significant improvement in school attendance, fatigue, physical functioning and self-reported improvements in 63% of those receiving CBT compared to 8% of those receiving treatment as usual. They also found that anxiety was related to non-recovery rates, although no specific scores were given for this [27, 34].

The common elements of all 5 cognitive behavioural and behavioural interventions appear to be the inclusion of a graded approach to managing activity, and employing strategies to address cognitive elements such as illness related beliefs and negative predictions about the future where necessary (see table 2 for details). Interventions varied considerably in the duration of treatment (12 weeks to 1 year), length of sessions (no direct therapist contact/30 minutes/60 minutes), and treatment modality (face-to-face, telephone, internet delivered modules with therapist e-consults).

In the study by Rowe, 71 patients were recruited into a RCT comparing IV gammaglobulin to a placebo[31]. Four domains were investigated, including school attendance, amount of school work attempted, amount of physical activities attempted and amount of social activities attempted. Anxiety was reduced in all participants at follow-up, both in those who were treated with the medication IV gammaglobulin and in those who received a placebo[31].

Outcome for children with CFS/ME in those who are anxious versus those who are not

There were no studies that assessed the outcome for children with CFS/ME who are anxious compared to those who were not. Some studies excluded those who were above a significant threshold for anxiety (Nijhof et al[27]) as shown in table 3.

Variation of outcome in children with CFS/ME and co-morbid anxiety

None of the studies compared the outcome between those with and without anxiety.

Table 3. Summary of outcomes for anxiety symptoms and other relevant findings for included studies

Authors (year)	Measure of Anxiety	Pre-treatment	Post-treatment (unless otherwise stated)	Statistical analysis of change in anxiety symptomatology	Summary of Other Relevant Findings
Chalder et al (2002)	HADS anxiety FQ	HADS anxiety – median 7, (IQ range 6.7-9.7) FQ agoraphobia 12.9 (8, 17.8) FQ blood/injury – 9.9 (5.7-14.2) FQ social – 12.2 (8.8-15.6) FQ total – 35.1 (26.2-43.9) FQ dysphoria – 11.7 (7.0-16.4)	6m follow-up HADS Anxiety –mean 0.5 IQ range 0.5-9 FQ agoraphobia 4.8 (2.2, 7.4) FQ blood/injury – 6.9 (2.9-10.8) FQ social – 8.5 (4.7-12.2) FQ total – 20.2 (11.5-28.9) FQ dysphoria – 6.3 (2.9-9.8)	Wilcoxon signed ranks test (significance 2 tailed) HADS anxiety – 2.02 (0.04) FQ agoraphobia – 2.85 (0.00) FQ blood/injury – 1.57 (0.12) FQ social – 1.42 (0.16) FQ total – 2.15 (0.03) FQ dysphoria – 1.58 (0.11)	The 20 participants who completed treatment had all returned to school at 6m follow-up, with 19 of 20 attending full time. Depression significantly improved, as did social adjustment.
Diaz-Caneja et al (2007)	MASC	Not stated. Raised levels of social anxiety and physical symptoms of anxiety.	Not stated although it is reported that anxiety improved	Not reported.	Report of a moderate response to treatment with the young person tolerating more activity. She had resumed contact with her friends, and although she still complained of tiredness and pain, she was attending classes daily.
Lloyd et al (2012)	SCAS	Baseline median 16.0 (interquartile range 10.8-35.0)	6 month follow-up mean 17.25 (SD 13.06)	Multi-level modelling and Wald tests Treatment effect estimate at 6m 0.49 Significance (two-tailed) 0.003, effect size 0.16.	Significant improvement in fatigue and school attendance, with reductions in depression and impairment and increased adjustment at 6m.
Nijhof et al (2012); Nijhof et al (2013)	STAIC	Intervention group: Mean 32.7 (SD 8.8) Control group: Mean 32.3 (SD 8.0)	Not stated.	At 6m, additional analyses of main findings with adjustments for anxiety, depression, and primary outcomes, had no effects on the results. When looking at factors related to recovery at 2.5y, anxiety OR 1.01 (95% CI 0.96-1.06), P = 0.66	Intervention (FITNET) was significantly more effective than the control (usual care) at 6 months—full school attendance (50 [75%] *vs* 10 [16%], relative risk 4·8, 95% CI 2·7–8·9; p<0·0001), absence of severe fatigue (57 [85%] *vs* 17 [27%], 3·2, 2·1–4·9; p<0·0001), and normal physical functioning (52 [78%] *vs* 13 [20%], 3·8, 2·3–6·3; p<0·0001). The short-term effectiveness of FITNET was maintained at 2.5y follow-up. At 2.5y follow-up, usual care led to similar recovery rates, although progress had taken longer to make.
Rimes et al (2007)	DAWBA	Not stated.	4 participants developed CFS/ME at follow-up (4 to 6m).	Not reported.	Of the 4 participants who developed CFS/ME over the follow-up period, 3 of 4 had at least 1 psychiatric diagnosis at baseline.
Rowe et al (1997)	SSTAQ	Reported as 1 group Mean 46.2 (SD	6m follow-up Mean 28.1 (SD 25.0) SE 5.9	T value (df) 2.63 (56) Sig p value 0.01	Significant mean functional improvement in both groups.

		24.4) SE 3.9 Range 0-98	Range 0-77		
Van de Putte, et al (2007)	SSTAQ	Mean 36.9 (SD 7.8)	Not stated.	Not reported.	47% of children 'fully recovered' (below score that is mean plus 2 S.D. of subjective fatigue distribution in healthy children).
Wright et al (2005)	HADS anxiety	Intervention: Mean 10.17 (SD 3.71) Control: Mean 6.80 (SD 3.56)	End of treatment Intervention: Mean 6.00 (3.63) Control: Mean 6.60 (SD 4.73)	Analysis of covariance for anxiety, controlling for baseline score. Difference -1.60 (-8.31-5.10) F 0.3 (df 1,8) P = 0.6	Activity (child and clinician rated) and school attendance improved markedly in the intervention (STAIRway) arm compared to little improvement in activity scores in the control (Pacing) arm, and a deterioration in school attendance. Global health (child and clinician rated) improved in both arms although more in the STAIRway arm than the pacing arm.

CBT = Cognitive Behaviour Therapy; CIS-20 = Checklist of Individual Strength; CFS = Chalder Fatigue Scale; DAWBA = Development and Well-being Assessment; FQ = Fear Questionnaire; HADS = Hospital Anxiety and Depression Scale; IQ = interquartile; MASC = Multidimensional Anxiety Scale for Children; SCAS = Spence Children's Anxiety Scale; SSTAQ = Spielberger State Trait Anxiety Questionnaire; STAIC = State-trait anxiety inventory for children

Discussion

This is the first review to investigate the treatment of anxiety in children with CFS/ME. From this review, we know that treatment using a cognitive behavioural or behavioural approach led to improvements in self-reported anxiety at follow-up. However, there is limited research in identifying other potentially effective treatment approaches, with only one study found that looked solely at medication (gammaglobulin)[31]. The existing research is also limited by the exclusion of patients with high levels of anxiety from some of the studies.

The strengths of this review include a thorough and wide-ranging search strategy by using a number of databases in addition to hand-searching articles. Two reviewers conducted each screening stage increasing the reliability of including/excluding studies. Expert help was sought from a librarian in conducting the search providing a higher chance of strong searching results. Furthermore, foreign language papers were included with the help of native speakers to aid in translation.

However, only eight studies were found with most having small sample sizes suggesting limited validity and reliability. Only three of the studies were RCTs and one excluded those with high anxiety scores[6, 27, 34]. This study that excluded participants with high anxiety scores limits the extent to which we can be confident that the findings in the study apply to those who are clinically anxious as well as those who are not[27].There is also a lack of any studies in children younger than 11 years old, and therefore, we don't know how best to tackle co-morbid anxiety in this group at all.

It is difficult to determine from the results of these studies whether anxiety scores have improved due to regression to the mean, anxiety reducing on its own without intervention or whether the treatment itself is having an effect. Anxiety may improve for CFS/ME paediatric patients by solely meeting a health care provider, as knowing they are receiving help may be enough to improve their symptoms. Alternatively, as the CFS/ME, and hence functioning, improves so may their anxiety as the cause behind it may be diminishing. Improvements in functioning may lead to naturalistic exposure to anxiety provoking situations, resulting in a habituation response. Alternatively, anxiety may improve on its own over time without any intervention. Therefore, it is not possible to ascertain the extent to which treatment was responsible for improvements, given the lack of robust studies, designed to specifically compare treatment for anxiety in paediatric CFS/ME patients to waiting list controls (or an alternative treatment/usual care).

The study by Rowe suggests that anxiety in CFS/ME may naturally decrease over time without active intervention[31]. This finding may be explained by the mean functional improvement that demonstrated a significant reduction in both groups; that is, anxiety might improve as a result of functionally improving. However, this is difficult to disentangle as both groups received information on education and social support services in this study, and this in itself may have been an active intervention that led to changes in functioning and anxiety[31].

For children without co-morbid conditions that present with anxiety, various treatment methods have shown to be effective, including CBT, bibliotherapy (parents

given a type of instruction manual to aid their children's' anxiety) and e-therapies (computerised programs)[36] . However, whether these therapies can be used effectively in CFS/ME is still relatively uncertain. As rates of anxiety are increased in children with CFS/ME, by remediating their fatigue, anxiety may decrease[8]. Therefore, although CBT techniques have been found to also reduce anxiety in CFS/ME, this may be as a consequence of successfully tackling their fatigue.

This review did not identify any studies that clarify the impact of anxiety on outcome in CFS/ME (with or without treatment), although one study did mention that anxiety was related to non-recovery without giving any further details. In adults with CFS/ME, one study has found that anxiety improved in CFS/ME patients receiving CBT, graded exercise therapy (GET) and activity management[37]. In other childhood chronic illnesses such as inflammatory bowel disease, CBT techniques have shown to be beneficial[38]. CBT has also been found to be effective for children with type 1 diabetes[39]. A systematic review concluded that despite weak evidence, CBT is beneficial in children with chronic physical illness and co-morbid anxiety[40]. On this basis, and as CBT has been found to be successful for anxiety in children in the general population, this does seem like the most promising approach. Further research to determine the impact of anxiety on recovery, and if necessary, to adapt CBT for CFS/ME to include anxiety management components, would be very beneficial.

Conclusion

Paediatric CFS/ME is a severe debilitating illness causing significant levels of school absence. About a third of children with CFS/ME have high levels of anxiety. We wanted to investigate which treatments are most effective in treating anxiety in these patients. Whilst CBT appears to result in lower levels of anxiety at follow up, there was insufficient evidence to conclude what the best treatment is for dealing with anxiety in paediatric CFS/ME patients.

Author's Contribution

ML designed the study protocol. SS and ML did the data search and data synthesis. SS drafted the manuscript and ML and EC reviewed and edited the manuscript. All authors reviewed the paper before submission.

List of Figures:

Figure 1. Systematic review flow chart (based on PRISMA guidelines)[41]

List of Abbreviations

CDC: Centres for Disease Control and prevention

CBT: Cognitive Behaviour Therapy

CFS: Chronic Fatigue Syndrome

CIS-20: Checklist Individual Strength-20

DAWBA: Development And Well Being Assessment

GAD: Generalised Anxiety Disorder

GET: Graded Exercise Therapy

HADS: The Hospital Anxiety and Depression Scale

MASC: Multidimensional Anxiety Scale for Children

ME: Myalgic Encephalomyelitis/Encephalopathy

NICE: National Institute for health and Clinical Excellence

RCTs: Randomised Controlled Trials

STAIC: State-Trait Anxiety Inventory for Children

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Conflict of interest statement: Esther Crawley is a medical advisor for the Association of Young People with ME (AYME) and the Sussex & Kent ME/CFS Society.

Registration
This review was registered on Prospero and the protocol is available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016043488

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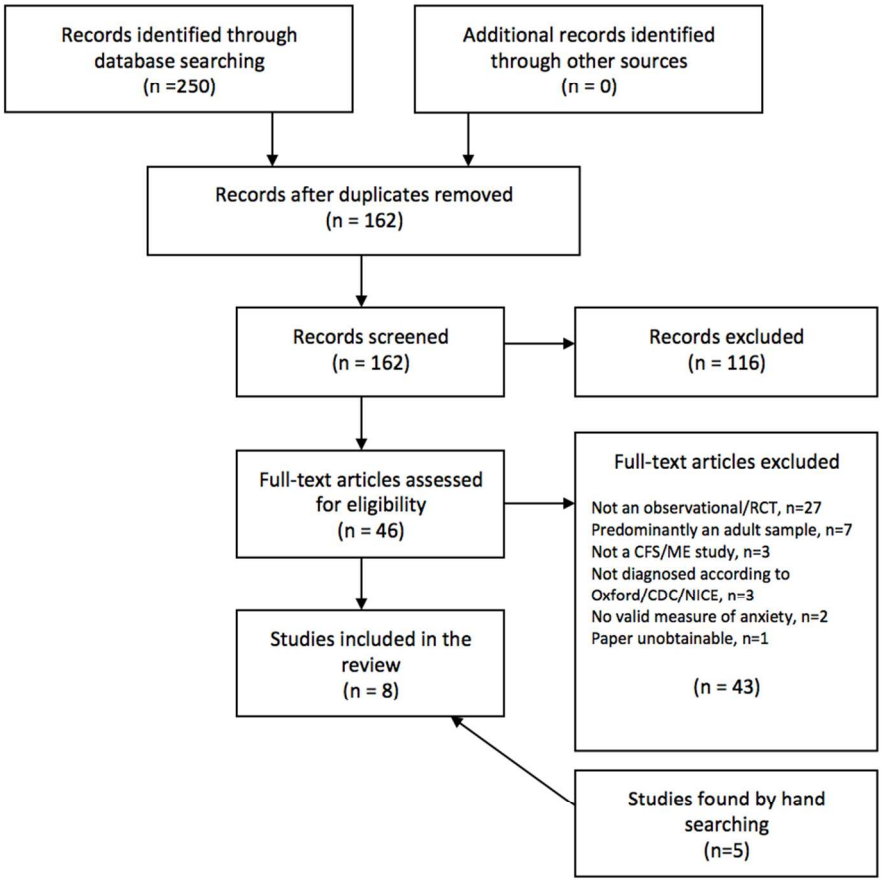

Figure 1. Systematic review flow chart (based on PRISMA guidelines)(41)

178x165mm (144 x 144 DPI)

Supplementary Information

Search Terms used in OVID and Cochrane Library

Paediatric	CFS/ME	Anxiety
adolesc*.tw preadolesc*.tw pre-adolesc*.tw boy*.tw girl*.tw child*.tw infan*.tw preschool*.tw pre-school*.tw juvenil*.tw minor*.tw pe?diatri*.tw pubescen*.tw pre-pubescen*.tw prepubescen*.tw puberty.tw teen*.tw young*.tw youth*.tw school*.tw high-school*.tw highschool*tw sibling*.tw schoolchild*.tw school child*.tw children.tw exp Adolescent exp child, preschool exp infant exp minors exp pediatr/ic	Chronic Fatigue Syndrome.tw myalgic encephal*.tw chronic fatigue syndrome*.mp. exp Fatigue Syndrome, Chronic/ myalgic encephal*.mp.	Anxiety disorder/ exp anxiety disorder Anxiety disorder/exp anxiety, separation Anxiety disorder/exp obsessive-compulsive disorder Anxiety disorder/exp phobic disorder Anxiety disorder/exp panic anxi*.tw generali?ed anxiety disorder.tw obsessive compulsive.tw OCD.tw Phobia*.tw Social anxiety.tw Separation anxiety.tw Panic.tw

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	✓
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	✓
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	✓
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	✓
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	✓
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	✓
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	✓
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	✓
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	✓
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	✓
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	✓
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	✓
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	✓
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	✓ For (a)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	✓
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	✓
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	✓
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	✓

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

What treatments work for anxiety in children with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME)?: systematic review

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Title: What treatments work for anxiety in children with Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis (CFS/ME)?: systematic review

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Word Count: 2893

Data sharing statement: This systematic review is based on published research only. There was no new data collected in this research.

Abstract

Objectives: Anxiety is more prevalent in children with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) than in the general population. A systematic review was carried out to identify which treatment methods are most effective for children with chronic fatigue syndrome and anxiety.

Setting: Systematic review

Participants: Studies were selected if participants were under 18, diagnosed with CFS/ME (using CDC, NICE or Oxford criteria) and had a valid assessment of anxiety. We included observational or Randomised Controlled Trials (RCT).

Results: The review found 9 papers from 8 studies that met the inclusion criteria. None of the studies specifically targeted anxiety but six studies tested an intervention and measured anxiety as a secondary outcome. Of these studies, 4 used a CBT-type approach to treat CFS/ME, one used a behavioural approach and one study compared a drug treatment, gammaglobulin, to a placebo. 3 of the CBT-type studies described an improvement in anxiety as did the trial testing gammaglobulin. As none of the studies stratified outcomes according to anxiety diagnostic status or severity we were unable to determine whether anxiety changed prognosis or whether treatments were equally effective in those with co-morbid anxiety compared to those without.

Conclusion: We do not know what treatment should be offered for children with both anxiety and CFS/ME. Further research is therefore required to answer this question.

Strengths and Limitations of the Study

- This systematic review identified publications investigating the treatment of anxiety in children with CFS/ME.
- Each article was screened and data was extracted independently by two reviewers.
- Foreign articles were included and translators were recruited to assist where necessary.
- However, the grey literature was not searched.
- The findings of the review are limited by the exclusion of children with high levels of anxiety from some treatment trials.

Registration

This review was registered on Prospero and the protocol is available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016043488

Keywords

Chronic fatigue syndrome; CFS/ME; Anxiety; paediatric; child and adolescent psychiatry

Background

Chronic Fatigue Syndrome (CFS)/Myalgic Encephalomyelitis (ME) is a chronic condition of unknown aetiology consisting of disabling fatigue, malaise, difficulty sleeping, joint/muscle aches and difficulty concentrating[1]. The prevalence of CFS/ME in teenagers varies from 0.5%-2.4% depending on the diagnostic criteria and methodology used[2-4]. CFS/ME can have a very debilitating impact on children with one study showing a 40% or less school attendance rate in 62% of children with CFS/ME[5]. Children experience difficulty concentrating and impairments in cognitive function which have a significant impact on education[6].

Anxiety is a relatively common mental health condition; in the general population it is estimated that 5-19% of all children suffer from anxiety[7]. Children with CFS/ME experience higher rates of anxiety than the normal population, with one study showing rates of 38% in teenage girls[8]. Specifically, separation anxiety and social phobia were found to be the most prevalent subtypes of anxiety in paediatric CFS/ME[8]. Children with a chronic illness might be more anxious as a reaction to being ill, a 'threatening environment' or other psychological factors as a result of their condition[9].

It is unclear whether children with CFS/ME develop anxiety as a result of their condition, whether psychological difficulties might pose a vulnerability to developing CFS/ME[2], or whether an external factor might increase the likelihood of an individual developing both anxiety and CFS/ME. Being diagnosed with CFS/ME has a severe impact on social life and attending school, which could potentially have a causative effect of depression and/or anxiety[10]. This may be compounded by the stigma surrounding CFS/ME and the inability to fully explain this illness[10, 11]. It is also possible that a biological mechanism is responsible for both the development of CFS/ME and anxiety, with some evidence of cortisol levels being implicated in CFS/ME in children and clear evidence of cortisol being linked to anxiety[12-14].

Anxiety may have a negative impact on recovery in paediatric CFS/ME by affecting an individual's ability to follow the evidence-based treatment for CFS/ME, which includes gradually increasing their activity levels. For example, in children, the aim of treatment for CFS/ME would be to gradually increase school attendance; however anxiety about going to school may prevent them from doing this. Therefore, co-morbid anxiety may need a specific treatment target in paediatric CFS/ME. The aims of this review are to establish what is known about treatment approaches for anxiety in children with CFS/ME and what is known about the impact of co-morbid anxiety on outcome in CFS/ME.

Methods

Data sources and search strategy

The search strategy for this systematic review incorporated the use of the Cochrane library and OVID to search the databases MEDLINE, EMBASE and psychINFO. It was designed to identify longitudinal studies (randomised trials and cohort studies), which included children with diagnosed CFS/ME and a measure of anxiety, to address the review questions. An information specialist was consulted about search strategy, resulting in a final list of search terms using Medical Subject Headings and free text (see supplementary material). Limits were applied according to the inclusion criteria. Final searches were conducted in July 2016. The full protocol can be found in the PROSPERO (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016043488). We did not revise the protocol after registration.

Study selection (inclusion and exclusion criteria)

We included observation studies or treatment trials which recruited participants with the following characteristics:

• Children <18 years of age
• Diagnosed with CFS/ME (chronic fatigue syndrome/myalgic encephalitis or myalgic encephalopathy) defined using CDC criteria (Fukuda 1994, 2004) or NICE (2007) or Oxford criteria
• Participants have completed a valid assessment of anxiety at baseline

Initial screening was by title and abstract to assess eligibility. Subsequently, full texts of the potentially eligible articles were reviewed to ascertain whether they met all the eligibility criteria. Two reviewers (from a pool of 5 reviewers, including SS, ML, VR, NL and AB) independently assessed papers at each stage. Differences in opinion were resolved by discussion, overseen by EC, with reference to the review protocol.

We did not search the grey literature but reference lists of all included articles were hand searched. Foreign studies were considered for inclusion with the help of native speakers to assist in translation and to determine whether the studies met the inclusion criteria.

Data extraction

For all included articles, data was extracted using a data extraction form, collecting information such as the CFS/ME definition used, treatment/interventions provided, definition of response, details of the setting of the study, how children were recruited for the study, date of the study and child characteristics (including age). Three reviewers (SS, ML, NL) independently carried out this process.

Data synthesis

There was insufficient comparable data to undertake a meta-analysis. Therefore, a narrative synthesis was undertaken.

Results

Identification of studies

A total of 1274 records were found by database searching, and after duplicates were removed, 1074 remained (figure 1). 223 articles were reviewed in full however only 9 papers were eligible from 8 studies. One foreign paper (Spanish) was included in this review, and a further three were considered ineligible at full text review (Dutch, German and Spanish).

Patient and study characteristics

Of the 8 studies, 5 were observational studies and 3 were Randomised Controlled Trials (RCTs). Anxiety was measured using self-report questionnaires including the Hospital Anxiety and Depression Scale (HADS)[15], the State-Trait Anxiety Inventory for Children (STAIC)[16], Spence Children's Anxiety Scale (SCAS)[17], and the Multidimensional Anxiety Scale for Children (MASC)[18]. 1 study used a diagnostic interview, the Development And Well-Being Assessment (DAWBA)[19] (table 1).

Sample sizes ranged from 1 to 135 (table 1) and ages ranged from 11-19 years. Most studies diagnosed participants according to the CDC criteria[20]. The majority of participants were female in all of the studies, which is consistent with the epidemiology of adolescent CFS/ME[21].

Table 1. Summary of methodology and study design of included studies

Authors (year)	Country	Design	Number of participants	Age - years	CFS/ME Diagnostic Criteria Applied	Measure of Anxiety	Intervention	Treatment specifically targeted at or adapted for anxiety?	Outcome stratified by anxious versus non-anxious?	Length of follow-up
Chalder, et al (2002)[22]	UK	Observational (outpatient treatment)	23 (18 at follow-up)	(Range 11-18, median 15)	Sharpe et al (1991)	HADS anxiety Fear questionnaire	CBT based rehabilitation programme. Up to 15 sessions, 1 hour in duration.	No	No	6m
Diaz-Caneja et al (2007)[23]	Spain	Observational (outpatient treatment) case study	1	15	Sharpe et al (1991)	MASC	CBT + fluoxetine (initially 10mg daily, increased after 1 week to 20 mg)	No	N/A	3m
Lloyd, et al (2012)[24] **Rimes et al (2014)**[25]	UK	Observational (outpatient treatment)	63 (52 at follow-up) 49 cases (24 at follow-up) 36 healthy controls	(Range 11-18, Median 15) Cases: mean 14.9 (SD 1.7) Controls: mean 15.0 (SD 1.7)	Sharpe et al (1991) Fukuda et al (1994) and Sharpe et al (1991)	SCAS	CBT via telephone based guided self-help – 6 fortnightly sessions, 30mins duration	No	No	6m
Nijhof et al (2012); Nijhof et al (2013)[26, 27]	Netherlands	Randomised control trial comparing internet-delivered CBT to usual care	135 (112 at long term follow-up)	Intervention group: mean 15.9 (SD 1.3) Control group: mean 15.8 (SD 1.3)	Fukuda et al (1994)	STAIC	Intervention: Internet delivered CBT consisting of psychoeducation and 21 modules, with parallel child and parent sessions. FITNET therapist individually tailored intervention and initially responded to emails weekly, decreasing to fortnightly. Mean treatment duration 26.2 weeks (SD 7.3). Control group: Treatment as usual including CBT (66%), rehabilitation treatment (22%), physical treatment (mostly graded exercise therapy; (49%), or alternative treatment (24%).	No	No	2.5 years
Rimes, et al (2007)[2]	UK	Observational (prospective, community)	1 case of CFS at Time 1; 4 cases	(Range 11-15)	Fukuda et al (1994)	DAWBA (interview)	None	N/A	N/A	4-6m

			CFS at identified at Time 2							
Rowe (1997)[28]	Australia	Randomised control trial comparing drug treatment to placebo	71 (70 at follow-up)	Intervention group: mean 15.3 (SD 2.0) Control group: mean 15.6 (SD 2.0)	Fukuda et al (1994)	SSTAQ	Intervention: 3 monthly infusions of gammaglobulin. Control: 3 monthly infusions of a dummy solution. Both arms received information on Visiting Teacher Service, Distance Education, and availability of Social Security support and had access to a support group.	No	No	6m
Van de Putte, et al (2007)[29]	Netherlands	Observational (prospective, community)	40 at baseline (36 at follow-up)	Mean 16.0 (SD 1.5)	Fukuda et al (1994)	SSTAQ	None	No	No	18m
Wright et al (2005)[30]	UK	Randomised control trial comparing Stairway to Health Intervention to Pacing	13 (11 at follow-up)	Intervention group (range 8.9 – 16.9) Control group (8.9-16.9)*	Sharpe et al (1991)	HADS anxiety	Intervention: STAIRway to Health intervention is a structured rehabilitation programme including conceptualising CFS as having both physical and psychological components, formulating and addressing vicious cycles around activity, sleep, social isolation, physical deconditioning, and developing adaptive coping strategies whilst challenging negative and unhelpful attributions about illness and the future. Control: Pacing focuses on limiting activity to the changing needs and responses of the body by avoiding overexertion and managing energy within an overall limit.	No	No	1y

CBT = Cognitive Behaviour Therapy; CIS-20 = Checklist of Individual Strength; CFS = Chalder Fatigue Scale; DAWBA = Development and Well-being Assessment; HADS = Hospital Anxiety and Depression Scale; MASC = Multidimensional Anxiety Scale for Children; SCAS = Spence Children's Anxiety Scale; SSTAQ = Spielberger State Trait Anxiety Questionnaire; STAIC = State-trait anxiety inventory for children
*Age range for all participants

Treatment in anxiety for children with CFS/ME

No studies specifically targeted anxiety in children with CFS/ME. Of the eight studies included, two[2, 29] were cross sectional population studies at two time points. These two studies did not test an intervention and were therefore uninformative for our research question.

Of the six treatment studies, four used a CBT approach, one used a behavioral approach and one used intravenous gammaglobulin. The primary outcomes included fatigue[22-24, 26, 27, 30], disability or function[28]and school attendance in[22, 24-27, 30]. All studies measured anxiety as a secondary outcome.

The common elements of all five cognitive behavioural and behavioural interventions appear to be the inclusion of a graded approach to managing activity, and employing strategies to address cognitive elements such as illness related beliefs and negative predictions about the future where necessary (see table 2 for details). Interventions varied considerably in the duration of treatment (12 weeks to 1 year), length of sessions (no direct therapist contact/30 minutes/60 minutes), and treatment modality (face-to-face, telephone, internet delivered modules with therapist e-consults).

Studies using a CBT approach:

The duration of CBT across the studies ranged from six 30 minute telephone sessions at fortnightly intervals[24, 25], to twenty-one internet session modules over 26 weeks[26, 27, 31]. In three of the four studies, the authors report that, anxiety improved with treatment, which suggests that cognitive behavioural treatment for CFS/ME may improve anxiety (table 3).

Nijhof et al's (2012, 2013) RCT compared internet-based CBT to traditional methods in 135 participants. The internet-based CBT, FITNET, includes psycho-educational modules for patients and parents in addition to CBT modules developed by the Expert Centre for Chronic Fatigue[26, 27]. Patients were able to send emails and therapists replied to 'e-consults' on the same day each week or depending the treatment plan. At 6 months, the study found a significant improvement in school attendance (full time school 75% in FITNET group compared to 16% in usual care group), fatigue and physical function in those receiving FITNET with 63% defined as "recovered" defined using primary and secondary outcome compared to 8% of those receiving treatment as usual.

In the observational cohort study by Chalder et al (2002), 23 participants were offered family based CBT. There was a significant improvement in anxiety (measured using the HADS) at 6 months (Median (IQR) 7 (6.7, 9.7) at assessment to 0.5 (0.5, 9)[22]. The family based CBT involved 15 fortnightly hourly sessions using a graded therapy method including a sleep routine and was implemented by patients and family with therapist guidance. The goal in this study was for children to return to full time education. Activity goals were set to include tasks such as walking, school work and attending social events. The activities were slowly increased and the aim to disassociating symptom relief with activity cessation. A sleep routine was also established in addition to changing perceptions of their illness to prevent negative thoughts.

Lloyd et al (2012) trialed a telephone self-help intervention involving 63 participants undergoing 6 fortnightly 30 minute sessions based on a CBT model that also showed a significant improvement in anxiety levels (treatment effect estimate -0.49 (CI -0.82, -0.17), p = 0.003)[24]. This approach addressed any fears the participants had towards the programme in addition to completing activity diaries and developing a better sleep routine. Fatigue and school attendance were the primary outcomes, with anxiety being a secondary outcome measure.

Diaz-Caneja et al (2007) reported a moderate response to combined CBT and fluoxetine treatment in a single case study (n=1)[23]. They found that with this approach there was increased tolerance to activity although the subject still felt tired. However, the specific components of treatment are not clear and treatment appears to have been ongoing at the time of writing the case study.

Non-CBT approaches:

Wright et al's (2005) study was an RCT comparing two behavioural approaches, one called 'pacing' and the other 'STAIRway to health'[30]. Thirteen children were randomised into either group with stratification for age, sex and mobility. The 'pacing' arm involved exercising to the child's limits whilst adapting to an individual's bodily needs. The 'STAIRway to health' arm was a structured tailored incremental rehabilitation programme that took a more holistic approach to CFS/ME aiming to treat both physical and psychological symptoms including nutrition, sleep, social activities and emotional issues[30]. The clinic appointments were weekly for one month, twice weekly for the next three months, three times a week for the following 2 months and four times weekly for the remaining 6 months. STAIRway had a greater emphasis on coping strategies to deal with both the physical and psychological implications of CFS/ME and showed a greater improvement in anxiety levels[30].

In the study by Rowe, 71 patients were recruited into a RCT comparing IV gammaglobulin to a placebo[28]. Four domains were investigated, including school attendance, amount of school work attempted, amount of physical activities attempted and amount of social activities attempted. Anxiety was reduced in all participants at 6 months follow-up, both in those who were treated with the medication IV gammaglobulin and in those who received a placebo[28].

Table 2. Details of components in provided in CBT and behavioural interventions

Study	Intervention	Duration and frequency
Chalder et al (2002)[22]	CBT-based rehabilitation programme including graded approach to increasing activity and establishing a sleep routine. Cognitive work was included where necessary.	Up to 15 hourly sessions, face-to-face.
Diaz-Caneja et al (2007)[23]	CBT (no further details given) + fluoxetine (initially 10mg daily, increased after 1 week to 20 mg).	No details given.
Lloyd et al (2012)[24] **Rimes et al (2014)**[25]	CBT which addressed unhelpful beliefs including fears about symptoms/activity. Activity diaries were used to establish a consistent routine and achieve a balance between activity and rest. The programme emphasised gradually increasing activities, including school, home, socialising and exercise, and establishing a regular sleep routine. Social and emotional problems addressed if time allowed.	Up to 6 x 30 minute sessions, by telephone, based on self-help manual.
Nijhof et al (2012); Nijhof et al (2013) [26, 27]	CBT in the FITNET program consisted of two sections, a psycho educational section and cognitive behavioural therapy section. Parents had parallel modules.	21 interactive modules delivered via the internet, with e-consultations from therapists.
Wright et al[30]	Structured Tailored Incremental Rehabilitation (STAIRway) programme - appears to be a behavioural intervention. Sessions were spent developing a holistic understanding of CFS, formulating the vicious cycles that exacerbate fatigue, including nutrition, sleep patterns, physical deconditioning, social isolation, school nonattendance, and emotional cycles. Adaptive coping strategies were developed, and negative attributions about illness and the future addressed. This was in addition to pacing activity to the changing needs and responses of the body by exercising to the point of tolerance, and avoiding overexertion.	Approximately 18 sessions over 1 year, beginning weekly and then gradually spacing out more. Face-to-face.

Outcome for children with CFS/ME in those who are anxious versus those who are not

There were no studies that assessed the outcome for children with CFS/ME who are anxious compared to those who were not. Some studies excluded those who were above a significant threshold for anxiety (Nijhof et al[26]) as shown in table 3.

Variation of outcome in children with CFS/ME and co-morbid anxiety

None of the studies compared the outcome between those with and without anxiety.

Table 3. Summary of outcomes for anxiety symptoms and other relevant findings for included studies

Authors (year)	Measure of Anxiety	Pre-treatment	Post-treatment (unless otherwise stated)	Statistical analysis of change in anxiety symptomatology	Summary of Other Relevant Findings
Chalder et al (2002)[32]	HADS anxiety FQ	HADS anxiety – median 7, (IQ range 6.7-9.7) FQ agoraphobia 12.9 (8, 17.8) FQ blood/injury – 9.9 (5.7-14.2) FQ social – 12.2 (8.8-15.6) FQ total – 35.1 (26.2-43.9) FQ dysphoria – 11.7 (7.0-16.4)	6m follow-up HADS Anxiety –mean 0.5 IQ range 0.5-9 FQ agoraphobia 4.8 (2.2, 7.4) FQ blood/injury – 6.9 (2.9-10.8) FQ social – 8.5 (4.7-12.2) FQ total – 20.2 (11.5-28.9) FQ dysphoria – 6.3 (2.9-9.8)	Wilcoxon signed ranks test (significance 2 tailed) HADS anxiety – 2.02 (0.04) FQ agoraphobia – 2.85 (0.00) FQ blood/injury – 1.57 (0.12) FQ social – 1.42 (0.16) FQ total – 2.15 (0.03) FQ dysphoria – 1.58 (0.11)	The 20 participants who completed treatment had all returned to school at 6m follow-up, with 19 of 20 attending full time. Depression significantly improved, as did social adjustment.
Diaz-Caneja et al (2007)[23]	MASC	Not stated. Raised levels of social anxiety and physical symptoms of anxiety.	Not stated although it is reported that anxiety improved	Not reported.	Report of a moderate response to treatment with the young person tolerating more activity. She had resumed contact with her friends, and although she still complained of tiredness and pain, she was attending classes daily.
Lloyd et al (2012)[24] **Rimes et al (2014)**[25]	SCAS	Baseline mean 22.84 (SD 17.18) Baseline median 16.0 (interquartile range 10.8-35.0) Cases: Baseline mean 22 (SD 17). Median 16.0 (interquartile range 9.0-34.0) Controls: Median 16.5 (interquartile range 8.0-22.8)	6 month follow-up mean 17.25 (SD 13.06) 6 month follow-up mean for CFS cases 17 (SD 14).	Multi-level modelling and Wald tests Treatment effect estimate at 6m 0.49 Significance (two-tailed) 0.003, effect size 0.16. T value (21)= 2.1. Significant p value 0.005	Significant improvement in fatigue and school attendance, with reductions in depression and impairment and increased adjustment at 6m. Adolescents with CFS had reduced cortisol excretion throughout the day compared to healthy controls. There was significant improvement in school attendance after treatment from 24% to 49%. There was reduction in fatigue after treatment, however the results were not significant.
Nijhof et al (2012); Nijhof et al (2013)[26, 27]	STAIC	Intervention group: Mean 32.7 (SD 8.8) Control group: Mean 32.3 (SD 8.0)	Not stated.	At 6m, additional analyses of main findings with adjustments for anxiety, depression, and primary outcomes, had no effects on the results. When looking at	Intervention (FITNET) was significantly more effective than the control (usual care) at 6 months—full school attendance (50 [75%] *vs* 10 [16%], relative risk 4·8, 95% CI 2·7–8·9; p<0·0001), absence of severe fatigue (57 [85%] *vs* 17 [27%], 3·2, 2·1–4·9; p<0·0001), and normal physical functioning (52 [78%] *vs* 13 [20%], 3·8, 2·3–6·3; p<0·0001). The short-term effectiveness of FITNET was maintained at 2.5y follow-up. At 2.5y follow-up, usual care led to similar

				factors related to recovery at 2.5y, anxiety OR 1.01 (95% CI 0.96-1.06), P = 0.66	recovery rates, although progress had taken longer to make.
Rimes et al (2007)[2]	DAWBA	Not stated.	4 participants developed CFS/ME at follow-up (4 to 6m).	Not reported.	Of the 4 participants who developed CFS/ME over the follow-up period, 3 of 4 had at least 1 psychiatric diagnosis at baseline.
Rowe et al (1997)[28]	SSTAQ	Reported as 1 group Mean 46.2 (SD 24.4) SE 3.9 Range 0-98	6m follow-up Mean 28.1 (SD 25.0) SE 5.9 Range 0-77	T value (df) 2.63 (56) Sig p value 0.01	Significant mean functional improvement in both groups.
Van de Putte, et al (2007)[29]	SSTAQ	Mean 36.9 (SD 7.8)	Not stated.	Not reported.	47% of children 'fully recovered' (below score that is mean plus 2 S.D. of subjective fatigue distribution in healthy children).
Wright et al (2005)[30]	HADS anxiety	Intervention: Mean 10.17 (SD 3.71) Control: Mean 6.80 (SD 3.56)	End of treatment Intervention: Mean 6.00 (3.63) Control: Mean 6.60 (SD 4.73)	Analysis of covariance for anxiety, controlling for baseline score. Difference -1.60 (-8.31-5.10) F 0.3 (df 1,8) P = 0.6	Activity (child and clinician rated) and school attendance improved markedly in the intervention (STAIRway) arm compared to little improvement in activity scores in the control (Pacing) arm, and a deterioration in school attendance. Global health (child and clinician rated) improved in both arms although more in the STAIRway arm than the pacing arm.

CBT = Cognitive Behaviour Therapy; CIS-20 = Checklist of Individual Strength; CFS = Chalder Fatigue Scale; DAWBA = Development and Well-being Assessment; FQ = Fear Questionnaire; HADS = Hospital Anxiety and Depression Scale; IQ = interquartile; MASC = Multidimensional Anxiety Scale for Children; SCAS = Spence Children's Anxiety Scale; SSTAQ = Spielberger State Trait Anxiety Questionnaire; STAIC = State-trait anxiety inventory for children

Discussion

This is the first systematic review to investigate the treatment of anxiety in children with CFS/ME. From this review, we know that treatment using a cognitive behavioural or behavioural approach led to improvements in self-reported anxiety at follow-up. However, the existing research is limited by the small sample sizes which are not powered to detect a treatment effect in the treatment of anxiety, inconsistency in the measurement of anxiety and the exclusion of patients with high levels of anxiety from some treatment trials[28].

The strengths of this review include a thorough and wide-ranging search strategy by using a number of databases in addition to hand-searching articles. Five reviewers carried out screening, with at least two reviewers screening each stage. An additional reviewer was consulted to resolve differences of opinion. Foreign language papers were included with the help of native speakers to aid in translation.

Only eight studies were found with most having small sample sizes. None were powered to determine treatment efficacy in those with CFS/ME and anxiety. Only three of the studies were RCTs and one excluded those with high anxiety scores[26-28, 30]making it difficult to investigate treatment effects in those with co-morbid anxiety. None of the studies included children who were 10 years old and younger and therefore we do not know about treatment efficacy in this group[26].

It is difficult to determine from the results of these studies whether anxiety scores have improved due to regression to the mean, anxiety reducing on its own without intervention or whether the treatment itself is having an effect. Improvements in disability may lead to exposure to anxiety provoking situations (for example school), resulting in a habituation response. Therefore, it is not possible to ascertain the extent to which treatment was responsible for improvements, given the lack of robust studies, designed to specifically compare treatment for anxiety in paediatric CFS/ME patients to waiting list controls (or an alternative treatment/usual care).

The study by Rowe suggests that anxiety in CFS/ME may naturally decrease over time without active intervention[28]. This finding may be explained by the mean functional improvement that demonstrated a significant reduction in both groups; that is, anxiety might improve as a result of functionally improving. However, this is difficult to disentangle as both groups received information on education and social support services in this study, and this in itself may have been an active intervention that led to changes in functioning and anxiety[28].

For children without co-morbid conditions that present with anxiety, various treatment methods have shown to be effective, including CBT, bibliotherapy (parents given a type of instruction manual to aid their children's' anxiety) and e-therapies (computerised programs)[33]. However, whether these therapies will be effective in paediatric CFS/ME is uncertain. As rates of anxiety are increased in children with CFS/ME, by remediating their fatigue, anxiety may decrease[8].

This review did not identify any studies that clarify the impact of anxiety on outcome in CFS/ME (with or without treatment). In adults with CFS/ME, one study has found that anxiety improved in CFS/ME patients receiving CBT, graded exercise therapy

(GET) and activity management[34]. In other childhood chronic illnesses such as inflammatory bowel disease, CBT techniques have shown to be beneficial[35]. CBT has also been found to be effective for children with type 1 diabetes[36]. A systematic review concluded that despite weak evidence, CBT is beneficial in children with chronic physical illness and co-morbid anxiety[37]. On this basis, and as CBT has been found to be successful for anxiety in children in the general population, this does seem like the most promising approach. Further research to determine the impact of anxiety on recovery, and if necessary, to adapt CBT for CFS/ME to include anxiety management components, would be beneficial.

Conclusion

Paediatric CFS/ME is a severe debilitating illness causing significant levels of school absence. About a third of children with CFS/ME have high levels of anxiety. We wanted to find out what was known about treatment approaches for anxiety in children with CFS/ME and what is known about the impact of co-morbid anxiety on outcome in CFS/ME. Whilst CBT appears to result in lower levels of anxiety at follow up, there was insufficient evidence to conclude what the best treatment is for dealing with anxiety in paediatric CFS/ME patients.

Author's Contribution

ML conceived the study and designed the study protocol. SS, ML, NL, VR and AB did the data search and data synthesis. EC resolved conflicts. SS drafted the manuscript and ML and EC reviewed and edited the manuscript. All authors reviewed the paper before submission.

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List of Abbreviations

CDC: Centres for Disease Control and prevention

CBT: Cognitive Behaviour Therapy

CFS: Chronic Fatigue Syndrome

CIS-20: Checklist Individual Strength-20

DAWBA: Development And Well Being Assessment

GAD: Generalised Anxiety Disorder

GET: Graded Exercise Therapy

HADS: The Hospital Anxiety and Depression Scale

MASC: Multidimensional Anxiety Scale for Children

ME: Myalgic Encephalomyelitis/Encephalopathy

NICE: National Institute for health and Clinical Excellence

RCTs: Randomised Controlled Trials

STAIC: State-Trait Anxiety Inventory for Children

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Conflict of interest statement: Esther Crawley is a medical advisor for the Sussex & Kent ME/CFS Society. There are no other conflicts of interest.

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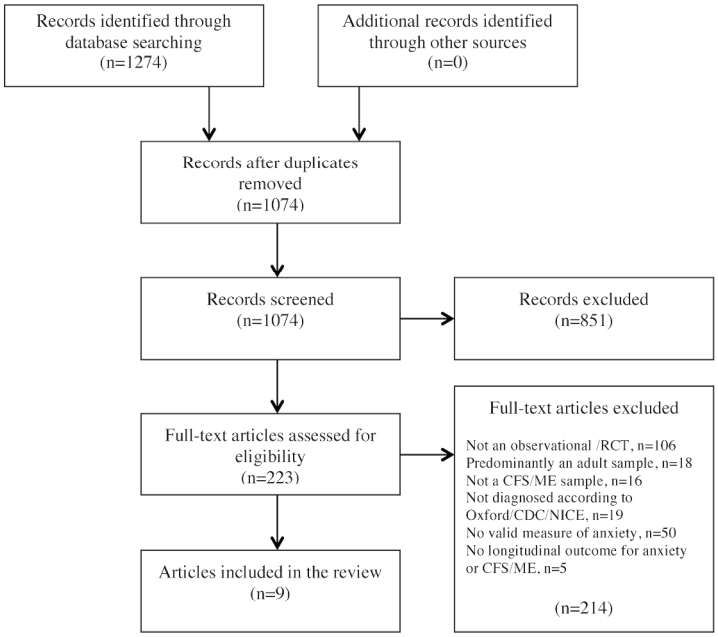

Figure 1. Systematic review flow chart (based on PRISMA guidelines)[38]

179x232mm (600 x 600 DPI)

Supplementary Information

Search Terms used in OVID and Cochrane Library

Paediatric	CFS/ME
adolesc*.tw preadolesc*.tw pre-adolesc*.tw boy*.tw girl*.tw child*.tw infan*.tw preschool*.tw pre-school*.tw juvenil*.tw minor*.tw p?ediatri*.tw pubescen*.tw pre-pubescen*.tw prepubescen*.tw puberty.tw teen*.tw young*.tw youth*.tw school*.tw high-school*.tw highschool*tw sibling*.tw schoolchild*.tw school child*.tw children.tw exp Adolescent exp child, preschool exp infant exp minors exp pediatr/ic	Chronic Fatigue Syndrome.tw myalgic encephal*.tw chronic fatigue syndrome*.mp. exp Fatigue Syndrome, Chronic/ myalgic encephal*.mp.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1 in title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 2 and 4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 4 and supplementary material
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 4/5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 4/5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 4/5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 4/5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 5 and Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 5 and Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 8-11 and Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 15
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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What treatments work for anxiety in children with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME)?: A Systematic Review

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Title: What treatments work for anxiety in children with Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis (CFS/ME)?: A Systematic Review

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Abstract

Objectives: Anxiety is more prevalent in children with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) than in the general population. A systematic review was carried out to identify which treatment methods are most effective for children with Chronic Fatigue Syndrome and anxiety.

Design: Systematic review using search terms entered into the Cochrane library and OVID to search the databases MEDLINE, EMBASE and psychINFO.

Participants: Studies were selected if participants were < 18 years old, diagnosed with CFS/ME (using CDC, NICE or Oxford criteria) and had a valid assessment of anxiety.

Interventions: We included observational studies and Randomised Controlled Trials (RCTs).

Comparison: Any or none.

Outcomes: Change in anxiety diagnostic status and/or change in anxiety severity on a validated measure of anxiety from pre-treatment to post-treatment.

Results: The review identified 9 papers from 8 studies that met the inclusion criteria. None of the studies specifically targeted anxiety but 6 studies tested an intervention and measured anxiety as a secondary outcome. Of these studies, 4 used a CBT-type approach to treat CFS/ME, one used a behavioural approach and one compared a drug treatment, gammaglobulin, to a placebo. Three of the CBT-type studies described an improvement in anxiety as did the trial of gammaglobulin. As none of the studies stratified outcomes according to anxiety diagnostic status or severity we were unable to determine whether anxiety changed prognosis or whether treatments were equally effective in those with co-morbid anxiety compared to those without.

Conclusion: We do not know what treatment should be offered for children with both anxiety and CFS/ME. Further research is therefore required to answer this question.

Strengths and Limitations of the Study

- This systematic review identified publications investigating the treatment of anxiety in children with CFS/ME.
- Each article was screened and the data was extracted independently by two reviewers.
- Foreign articles were included and translators were recruited to assist where necessary.
- However, the grey literature was not searched.
- The findings of the review are limited by the exclusion of children with high levels of anxiety from some treatment trials.

Registration

This review was registered on Prospero and the protocol is available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016043488

Keywords
Chronic fatigue syndrome; CFS/ME; Anxiety; paediatric; child and adolescent psychiatry

Background

Chronic Fatigue Syndrome (CFS)/Myalgic Encephalomyelitis (ME) is a chronic condition of unknown aetiology consisting of disabling fatigue, malaise, difficulty sleeping, joint/muscle aches and difficulty concentrating[1]. The prevalence of CFS/ME in teenagers varies from 0.5%-2.4% depending on the diagnostic criteria and methodology used[2-4]. CFS/ME can have a very debilitating impact on children with one study showing a ≤ 40% school attendance rate in almost two-thirds (62%) of children with CFS/ME[5]. Furthermore, children with CFS/ME experience difficulty concentrating and impairments in cognitive function which have a significant impact on their learning and education[6].

Anxiety is a relatively common mental health condition; in the general population it is estimated that 5-19% of all children suffer from anxiety[7]. Children with CFS/ME experience higher rates of anxiety than the normal population, with one study showing rates of 38% in teenage girls[8]. Specifically, separation anxiety and social phobia were found to be the most prevalent subtypes of anxiety in paediatric CFS/ME[8]. Children with a chronic illness might be more anxious as a reaction to being ill, the 'threatening environment' of a chronic illness, or other psychological factors as a result of their condition[9].

It is unclear as to whether children with CFS/ME develop anxiety as a result of their condition, or whether psychological difficulties might pose a vulnerability to developing CFS/ME[2], or whether an external factor might increase the likelihood of an individual developing both anxiety and CFS/ME. Being diagnosed with CFS/ME has a substantial impact on social and academic life, which could potentially contribute to the development of distress, including depression and/or anxiety[10]. This may be compounded by the stigma surrounding CFS/ME and the inability to fully explain this illness, resulting in uncertainty[10, 11]. It is also possible that a biological mechanism is responsible for both the development of CFS/ME and anxiety, with some evidence of cortisol levels being implicated in CFS/ME in children and clear evidence of cortisol being linked to anxiety[12-14].

Anxiety may have a negative impact on recovery in paediatric CFS/ME by affecting an individual's ability to follow the evidence-based treatment for CFS/ME, which includes gradually increasing their activity levels. For example, in children, the aim of treatment for CFS/ME would be to gradually increase school attendance; however anxiety about going to school may prevent them from doing this. Therefore, co-morbid anxiety may need to be a specific treatment target in paediatric CFS/ME. The aims of this review are to establish what is known about treatment approaches for anxiety in children with CFS/ME and what is known about the impact of co-morbid anxiety on outcome in CFS/ME.

Methods

Data sources and search strategy

The search strategy for this systematic review incorporated the use of the Cochrane library and OVID to search the databases MEDLINE, EMBASE and psychINFO. The search strategy was designed with input from an information specialist, to include the concepts 'paediatric' and 'CFS/ME'. Limits were applied according to the inclusion criteria. Final searches were conducted in July 2016. The full protocol can be found in PROSPERO (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016043488). The protocol was not revised after registration, although the search terms were slightly amended, and the final search terms are available as supplementary information.

The grey literature was not searched, but the reference lists of all the included articles were hand searched. Foreign studies were considered for inclusion with the help of native speakers who assisted in the translation of these to determine whether the studies met the inclusion criteria.

I*nclusion and Exclusion criteria*

Studies were included if they met the following criteria:

Participants:

• Children <18 years of age

• Diagnosed with CFS/ME (chronic fatigue syndrome/myalgic encephalitis or myalgic encephalopathy) defined using CDC criteria (Fukuda 1994, 2004) or NICE (2007) or Oxford criteria

Interventions:

- Longitudinal study (treatment trial or observational cohort study)

Comparison:

- Any or none.

Outcomes:

- Study included a validated assessment of anxiety at baseline, and repeated measures for either anxiety or fatigue on a validated scale.

Study Selection

Initial screening was by title and abstract to assess eligibility. Subsequently, full texts of the potentially eligible articles were reviewed to ascertain whether they met all the eligibility criteria. Two reviewers (from a pool of 5 reviewers, including SS, ML, VR, NL and AB) independently assessed papers at each stage. Differences in opinion were resolved by discussion, overseen by EC, with reference to the review protocol.

Data extraction

For all included articles, data was extracted using a data extraction form, collecting information such as the CFS/ME definition used, treatment/interventions provided, definition of response, details of the setting of the study, how children were recruited

for the study, date of the study and child characteristics (including age). Three reviewers (SS, ML, NL) independently carried out this process.

Quality Assessment

Two reviewers independently assessed the quality of the studies included using the Cochrane risk of bias assessment tool as well as Critical Appraisal Skills Programme tools [15-17]. This was done for both observational studies and RCTs.

Data synthesis

There was insufficient comparable data to undertake a meta-analysis. Therefore, a narrative synthesis was undertaken.

Results

Identification of studies

A total of 1274 records were found by database searching, and after duplicates were removed, 1074 remained (figure 1). 223 articles were reviewed in full however only 9 papers were eligible from 8 studies. One foreign paper (Spanish) was included in this review, and a further three were considered ineligible at full text review (Dutch, German and Spanish).

Quality Assessment

There were 5 observational studies and 3 RCTs that were included in this systematic review. Most of the studies had a clear focused issue, although none of the included studies specifically focused on change in anxiety in paediatric CFS/ME as their primary outcome. The participants were recruited in an acceptable way for most studies. The RCTs were judged most robust and least at risk of bias; the participant groups were comparable at the point of randomization and the groups were also treated equally apart from the experimental treatment under investigation. One RCT used a placebo[18], whilst the other two used an active treatment comparison (treatment as usual)[6, 19-21]. For the observational studies, one paper, which was a case study, had significant methodological limitations, and therefore a high risk of bias[22]. For the remainder of the observational studies[2, 23-25], risk of bias was either low or unclear; exposure and outcome were measured accurately to reduce bias in most studies and follow-up was long enough. The quality assessment is available as supplementary information.

Patient and study characteristics

Anxiety was measured using self-report questionnaires including the Hospital Anxiety and Depression Scale (HADS)[26], the State-Trait Anxiety Inventory for Children (STAIC)[27], Spence Children's Anxiety Scale (SCAS)[28], and the Multidimensional Anxiety Scale for Children (MASC)[29]. One study used a diagnostic interview, the Development And Well-Being Assessment (DAWBA)[30] (see table 1).

Sample sizes ranged from 1 to 135 (see table 1) and ages ranged from 11-19 years. Most studies diagnosed participants according to the CDC criteria[31]. The majority of

participants were female in all of the studies, which is consistent with the epidemiology of adolescent CFS/ME[32].

Table 1. Summary of methodology and study design of included studies

Authors (year)	Country	Design	Number of participants	Age - years	CFS/ME Diagnostic Criteria Applied	Measure of Anxiety	Intervention	Treatment specifically targeted at or adapted for anxiety?	Outcome stratified by anxious versus non-anxious?	Length of follow-up
Chalder, et al (2002)[23]	UK	Observational (outpatient treatment)	23 (18 at follow-up)	(Range 11-18, median 15)	Sharpe et al (1991)	HADS anxiety Fear questionnaire	CBT based rehabilitation programme. Up to 15 sessions, 1 hour in duration.	No	No	6m
Diaz-Caneja et al (2007)[22]	Spain	Observational (outpatient treatment) case study	1	15	Sharpe et al (1991)	MASC	CBT + fluoxetine (initially 10mg daily, increased after 1 week to 20 mg)	No	N/A	3m
Lloyd, et al (2012)[24] **Rimes et al (2014)**[33]	UK	Observational (outpatient treatment)	63 (52 at follow-up) 49 cases (24 at follow-up) 36 healthy controls	(Range 11-18, Median 15) Cases: mean 14.9 (SD 1.7) Controls: mean 15.0 (SD 1.7)	Sharpe et al (1991) Fukuda et al (1994) and Sharpe et al (1991)	SCAS	CBT via telephone based guided self-help – 6 fortnightly sessions, 30mins duration	No	No	6m
Nijhof et al (2012); Nijhof et al (2013)[34, 21]	Netherlands	Randomised control trial comparing internet-delivered CBT to usual care	135 (112 at long term follow-up)	Intervention group: mean 15.9 (SD 1.3) Control group: mean 15.8 (SD 1.3)	Fukuda et al (1994)	STAIC	Intervention: Internet delivered CBT consisting of psychoeducation and 21 modules, with parallel child and parent sessions. FITNET therapist individually tailored intervention and initially responded to emails weekly, decreasing to fortnightly. Mean treatment duration 26.2 weeks (SD 7.3). Control group: Treatment as usual including CBT (66%), rehabilitation treatment (22%), physical treatment (mostly graded exercise therapy; (49%), or alternative treatment (24%).	No	No	2.5 years
Rimes, et al (2007)[2]	UK	Observational (prospective, community)	1 case of CFS at Time 1; 4 cases	(Range 11-15)	Fukuda et al (1994)	DAWBA (interview)	None	N/A	N/A	4-6m

			CFS at identified at Time 2							
Rowe (1997)[22]	Australia	Randomised control trial comparing drug treatment to placebo	71 (70 at follow-up)	Intervention group: mean 15.3 (SD 2.0) Control group: mean 15.6 (SD 2.0)	Fukuda et al (1994)	SSTAQ	Intervention: 3 monthly infusions of gammaglobulin. Control: 3 monthly infusions of a dummy solution. Both arms received information on Visiting Teacher Service, Distance Education, and availability of Social Security support and had access to a support group.	No	No	6m
Van de Putte, et al (2007)[25]	Netherlands	Observational (prospective, community)	40 at baseline (36 at follow-up)	Mean 16.0 (SD 1.5)	Fukuda et al (1994)	SSTAQ	None	No	No	18m
Wright et al (2005)[19]	UK	Randomised control trial comparing Stairway to Health Intervention to Pacing	13 (11 at follow-up)	Intervention group (range 8.9 – 16.9) Control group (8.9-16.9)*	Sharpe et al (1991)	HADS anxiety	Intervention: STAIRway to Health intervention is a structured rehabilitation programme including conceptualising CFS as having both physical and psychological components, formulating and addressing vicious cycles around activity, sleep, social isolation, physical deconditioning, and developing adaptive coping strategies whilst challenging negative and unhelpful attributions about illness and the future. Control: Pacing focuses on limiting activity to the changing needs and responses of the body by avoiding overexertion and managing energy within an overall limit.	No	No	1y

CBT = Cognitive Behaviour Therapy; CIS-20 = Checklist of Individual Strength; CFS = Chalder Fatigue Scale; DAWBA = Development and Well-being Assessment; HADS = Hospital Anxiety and Depression Scale; MASC = Multidimensional Anxiety Scale for Children; SCAS = Spence Children's Anxiety Scale; SSTAQ = Spielberger State Trait Anxiety Questionnaire; STAIC = State-trait anxiety inventory for children
*Age range for all participants

Treatment in anxiety for children with CFS/ME

No studies specifically targeted anxiety in children with CFS/ME. Of the eight studies included, two[2, 25] were longitudinal observational cohort studies. These two studies did not test an intervention and were therefore uninformative for establishing what is known about treatments for children with CFS/ME and anxiety.

Of the six treatment studies, four used a CBT approach, one used a behavioral approach and one used intravenous (IV) gammaglobulin. The primary outcomes included fatigue[19, 21-24, 34], disability or function[22] and school attendance in[19, 21, 23, 24, 33, 34]. All studies measured anxiety as a secondary outcome.

The common elements of all five cognitive behavioural and behavioural interventions appear to be the inclusion of a graded approach to managing activity, and employing strategies to address cognitive elements such as illness related beliefs and negative predictions about the future where necessary (see table 2 for details). Interventions varied considerably in the duration of treatment (12 weeks to 1 year), length of sessions (no direct therapist contact/30 minutes/60 minutes), and treatment modality (face-to-face, telephone, internet delivered modules with therapist e-consults).

Studies using a CBT approach:

The duration of CBT across the studies ranged from six 30 minute telephone sessions at fortnightly intervals[24, 33], to twenty-one internet session modules over 26 weeks[21, 26, 34]. In three of the four studies, the authors report that, anxiety improved with treatment, which suggests that cognitive behavioural treatment for CFS/ME may improve anxiety (table 3).

Nijhof et al's (2012, 2013) RCT compared internet-based CBT to traditional methods in 135 participants. The internet-based CBT, FITNET, includes psycho-educational modules for patients and parents in addition to CBT modules developed by the Expert Centre for Chronic Fatigue[21, 34]. Patients were able to send emails and therapists replied to 'e-consults' on the same day each week or according to the treatment plan. At 6 months post randomisation, the study demonstrated a significant improvement in school attendance (full time school 75% in FITNET group compared to 16% in usual care group), fatigue and physical function in those receiving the FITNET intervention with 63% defined as "recovered" compared to 8% of those receiving treatment as usual.

In the treatment study by Chalder et al (2002), 23 participants were offered family based CBT. There was a significant improvement in anxiety (measured using the HADS) at 6 months (Median (IQR) 7 (6.7, 9.7) at assessment to 0.5 (0.5, 9)[23]. The family based CBT involved 15 fortnightly hourly sessions using a graded therapy method including a sleep routine and was implemented by patients and family with therapist guidance. The goal in this study was for children to return to full time education. Activity goals were set to include tasks such as walking, school work and attending social events. The activities were slowly increased and the aim to disassociating symptom relief with activity cessation. A sleep routine was also established in addition to changing perceptions of their illness to prevent negative thoughts.

Lloyd et al (2012) trialed a telephone self-help intervention involving 63 participants undergoing 6 fortnightly 30 minute sessions based on a CBT model that also showed a significant improvement in anxiety levels (treatment effect estimate -0.49 (CI -0.82, -0.17), p = 0.003)[24]. This approach addressed any fears the participants had towards the programme in addition to completing activity diaries and developing a better sleep routine. Fatigue and school attendance were the primary outcomes, with anxiety being a secondary outcome measure.

Diaz-Caneja et al (2007) reported a moderate response to combined CBT and fluoxetine treatment in a single case study (n=1)[22]. They found that with this approach, there was increased tolerance to activity although the subject still felt tired. However, the specific components of treatment are not clear and the treatment appears to have been ongoing at the time of writing the case study.

Study using a behavioural approach:

Wright et al's (2005) study was an RCT comparing two behavioural approaches, one called 'pacing' and the other 'STAIRway to health'[19]. Thirteen children were randomised into the treatment groups with stratification for age, sex and mobility. The 'pacing' arm involved exercising to the child's limits whilst adapting to an individual's bodily needs. The 'STAIRway to health' arm was a structured tailored incremental rehabilitation programme that took a more holistic approach to CFS/ME aiming to treat both physical and psychological symptoms including nutrition, sleep, social activities and emotional issues[19]. The clinic appointments were weekly for one month, fortnightly for the next 3 months, every third week for two months, and every 4 weeks for 6 months. . STAIRway had a greater emphasis on coping strategies to deal with both the physical and psychological implications of CFS/ME and showed a greater improvement in anxiety levels[19].

Study using a pharmacological treatment:

In the study by Rowe, 71 patients were recruited into a RCT comparing IV gammaglobulin to a placebo[22]. Four domains were investigated, including school attendance, amount of school work attempted, amount of physical activities attempted and amount of social activities attempted. Anxiety reduced in all participants at 6 months follow-up, both in those who were treated with the medication IV gammaglobulin and in those who received a placebo[22].

Table 2. Details of components in provided in CBT and behavioural interventions

Study	Intervention	Duration and frequency
Chalder et al (2002)[23]	CBT-based rehabilitation programme including graded approach to increasing activity and establishing a sleep routine. Cognitive work was included where necessary.	Up to 15 hourly sessions, face-to-face.
Diaz-Caneja et al (2007)[22]	CBT (no further details given) + fluoxetine (initially 10mg daily, increased after 1 week to 20 mg).	No details given.
Lloyd et al (2012)[24] **Rimes et al (2014)**[33]	CBT which addressed unhelpful beliefs including fears about symptoms/activity. Activity diaries were used to establish a consistent routine and achieve a balance between activity and rest. The programme emphasised gradually increasing activities, including school, home, socialising and exercise, and establishing a regular sleep routine. Social and emotional problems addressed if time allowed.	Up to 6 x 30 minute sessions, by telephone, based on self-help manual.
Nijhof et al (2012); Nijhof et al (2013) [34, 21]	CBT in the FITNET program consisted of two sections, a psycho educational section and cognitive behavioural therapy section. Parents had parallel modules.	21 interactive modules delivered via the internet, with e-consultations from therapists.
Wright et al[19]	Structured Tailored Incremental Rehabilitation (STAIRway) programme - appears to be a behavioural intervention. Sessions were spent developing a holistic understanding of CFS, formulating the vicious cycles that exacerbate fatigue, including nutrition, sleep patterns, physical deconditioning, social isolation, school nonattendance, and emotional cycles. Adaptive coping strategies were developed, and negative attributions about illness and the future addressed. This was in addition to pacing activity to the changing needs and responses of the body by exercising to the point of tolerance, and avoiding overexertion.	Approximately 18 sessions over 1 year, beginning weekly and then gradually spacing out more. Face-to-face.

Outcome for children with CFS/ME in those who are anxious versus those who are not

Neither the longitudinal observational cohort studies, nor the treatment studies that assessed the outcome for children with CFS/ME who are anxious compared to those who were not. Some studies excluded those who were above a significant threshold for anxiety (Nijhof et al[34]) as shown in table 3.

Variation of outcome in children with CFS/ME and co-morbid anxiety

None of the studies compared the outcome between those with and without anxiety.

Table 3. Summary of outcomes for anxiety symptoms and other relevant findings for included studies

Authors (year)	Measure of Anxiety	Pre-treatment	Post-treatment (unless otherwise stated)	Statistical analysis of change in anxiety symptomatology	Summary of Other Relevant Findings
Chalder et al (2002)[23]	HADS anxiety FQ	HADS anxiety – median 7, (IQ range 6.7-9.7) FQ agoraphobia 12.9 (8, 17.8) FQ blood/injury – 9.9 (5.7-14.2) FQ social – 12.2 (8.8-15.6) FQ total – 35.1 (26.2-43.9) FQ dysphoria – 11.7 (7.0-16.4)	6m follow-up HADS Anxiety –mean 0.5 IQ range 0.5-9 FQ agoraphobia 4.8 (2.2, 7.4) FQ blood/injury – 6.9 (2.9-10.8) FQ social – 8.5 (4.7-12.2) FQ total – 20.2 (11.5-28.9) FQ dysphoria – 6.3 (2.9-9.8)	Wilcoxon signed ranks test (significance 2 tailed) HADS anxiety – 2.02 (0.04) FQ agoraphobia – 2.85 (0.00) FQ blood/injury – 1.57 (0.12) FQ social – 1.42 (0.16) FQ total – 2.15 (0.03) FQ dysphoria – 1.58 (0.11)	The 20 participants who completed treatment had all returned to school at 6m follow-up, with 19 of 20 attending full time. Depression significantly improved, as did social adjustment.
Diaz-Caneja et al (2007)[22]	MASC	Not stated. Raised levels of social anxiety and physical symptoms of anxiety.	Not stated although it is reported that anxiety improved	Not reported.	Report of a moderate response to treatment with the young person tolerating more activity. She had resumed contact with her friends, and although she still complained of tiredness and pain, she was attending classes daily.
Lloyd et al (2012)[24] **Rimes et al (2014)**[33]	SCAS	Baseline mean 22.84 (SD 17.18) Baseline median 16.0 (interquartile range 10.8-35.0) Cases: Baseline mean 22 (SD 17). Median 16.0 (interquartile range 9.0-34.0) Controls: Median 16.5 (interquartile range 8.0-22.8)	6 month follow-up mean 17.25 (SD 13.06) 6 month follow-up mean for CFS cases 17 (SD 14).	Multi-level modelling and Wald tests Treatment effect estimate at 6m 0.49 Significance (two-tailed) 0.003, effect size 0.16. T value (21)= 2.1. Significant p value 0.005	Significant improvement in fatigue and school attendance, with reductions in depression and impairment and increased adjustment at 6m. Adolescents with CFS had reduced cortisol excretion throughout the day compared to healthy controls. There was significant improvement in school attendance after treatment from 24% to 49%. There was reduction in fatigue after treatment, however the results were not significant.
Nijhof et al (2012); Nijhof et al (2013)[34, 21]	STAIC	Intervention group: Mean 32.7 (SD 8.8) Control group: Mean 32.3 (SD 8.0)	Not stated.	At 6m, additional analyses of main findings with adjustments for anxiety, depression, and primary outcomes, had no effects on the results. When looking at	Intervention (FITNET) was significantly more effective than the control (usual care) at 6 months—full school attendance (50 [75%] *vs* 10 [16%], relative risk 4·8, 95% CI 2·7–8·9; p<0·0001), absence of severe fatigue (57 [85%] *vs* 17 [27%], 3·2, 2·1–4·9; p<0·0001), and normal physical functioning (52 [78%] *vs* 13 [20%], 3·8, 2·3–6·3; p<0·0001). The short-term effectiveness of FITNET was maintained at 2.5y follow-up. At 2.5y follow-up, usual care led to similar

				factors related to recovery at 2.5y, anxiety OR 1.01 (95% CI 0.96-1.06), P = 0.66	recovery rates, although progress had taken longer to make.
Rimes et al (2007)[2]	DAWBA	Not stated.	4 participants developed CFS/ME at follow-up (4 to 6m).	Not reported.	Of the 4 participants who developed CFS/ME over the follow-up period, 3 of 4 had at least 1 psychiatric diagnosis at baseline.
Rowe et al (1997)[22]	SSTAQ	Reported as 1 group Mean 46.2 (SD 24.4) SE 3.9 Range 0-98	6m follow-up Mean 28.1 (SD 25.0) SE 5.9 Range 0-77	T value (df) 2.63 (56) Sig p value 0.01	Significant mean functional improvement in both groups.
Van de Putte, et al (2007)[25]	SSTAQ	Mean 36.9 (SD 7.8)	Not stated.	Not reported.	47% of children 'fully recovered' (below score that is mean plus 2 S.D. of subjective fatigue distribution in healthy children).
Wright et al (2005)[19]	HADS anxiety	Intervention: Mean 10.17 (SD 3.71) Control: Mean 6.80 (SD 3.56)	End of treatment Intervention: Mean 6.00 (3.63) Control: Mean 6.60 (SD 4.73)	Analysis of covariance for anxiety, controlling for baseline score. Difference -1.60 (-8.31-5.10) F 0.3 (df 1,8) P = 0.6	Activity (child and clinician rated) and school attendance improved markedly in the intervention (STAIRway) arm compared to little improvement in activity scores in the control (Pacing) arm, and a deterioration in school attendance. Global health (child and clinician rated) improved in both arms although more in the STAIRway arm than the pacing arm.

CBT = Cognitive Behaviour Therapy; CIS-20 = Checklist of Individual Strength; CFS = Chalder Fatigue Scale; DAWBA = Development and Well-being Assessment; FQ = Fear Questionnaire; HADS = Hospital Anxiety and Depression Scale; IQ = interquartile; MASC = Multidimensional Anxiety Scale for Children; SCAS = Spence Children's Anxiety Scale; SSTAQ = Spielberger State Trait Anxiety Questionnaire; STAIC = State-trait anxiety inventory for children

Discussion

This is the first systematic review to investigate the outcomes of and treatment of children with CFS/ME who are also anxious. From this review, we know that treatment using a cognitive behavioural or behavioural approach led to improvements in self-reported anxiety at follow-up. However, the existing research is limited by the small sample sizes which are not powered to detect a treatment effect in the treatment of anxiety, inconsistency in the measurement of anxiety and the exclusion of patients with high levels of anxiety from some treatment trials[22].

The strengths of this review include a thorough and wide-ranging search strategy by using a number of databases in addition to hand-searching articles. Five reviewers carried out screening, with at least two reviewers screening each stage. An additional reviewer was consulted to resolve differences of opinion. Foreign language papers were included with the help of native speakers to aid in translation.

Only eight studies were found with most having small sample sizes. None were powered to determine treatment efficacy in those with CFS/ME and anxiety. Only three of the studies were RCTs and one excluded those with high anxiety scores[18, 19, 21, 34]making it difficult to investigate treatment effects in those with co-morbid anxiety. None of the studies included children who were 10 years old and younger and therefore we do not know about treatment efficacy in this group[34].

It is difficult to determine from the results of these studies whether anxiety scores have improved due to regression to the mean, anxiety reducing on its own without intervention or whether the treatment itself is having an effect. Improvements in functioning may lead to increased exposure to anxiety provoking situations (for example, school), resulting in a habituation response. Therefore, it is not possible to ascertain the extent to which treatment was responsible for improvements, given the lack of robust studies, designed to specifically compare treatment for anxiety in paediatric CFS/ME patients to waiting list controls (or an alternative treatment/usual care).

The improvements in anxiety reported in the study by Rowe in both the pharmacological treatment arm and the placebo arm suggests that anxiety in CFS/ME may naturally decrease over time without active intervention[22]. This finding may be explained by the mean functional improvement that demonstrated a significant reduction in both groups; that is, anxiety might improve as a result of functionally improving. However, this is difficult to disentangle as both groups received information on education and social support services in this study, and this in itself may have been an active intervention that led to changes in functioning and anxiety[22].

For children without co-morbid physical health conditions who present for treatment of anxiety, various interventions have shown to be effective, including CBT, bibliotherapy (parents given a type of instruction manual to aid their children's' anxiety) and e-therapies (computerised programs)[35]. However, whether these therapies will be effective in paediatric CFS/ME is uncertain. As rates of anxiety are increased in children with CFS/ME, by remediating their fatigue, anxiety may decrease[8].

This review did not identify any studies that clarify the impact of anxiety on outcome in CFS/ME (with or without treatment). In adults with CFS/ME, one study has found that anxiety improved in CFS/ME patients receiving CBT, graded exercise therapy (GET) and activity management[36]. In other childhood chronic illnesses such as inflammatory bowel disease, CBT techniques have shown to be beneficial[37]. CBT has also been found to be effective for children with type 1 diabetes[38]. A systematic review concluded that despite weak evidence, CBT is beneficial in children with chronic physical illness and co-morbid anxiety[39]. On this basis, and as CBT has been found to be successful for anxiety in children in the general population, this does seem like the most promising approach. Further research to determine the impact of anxiety on recovery, and if necessary, to adapt CBT for CFS/ME to include anxiety management components, would be beneficial.

Conclusion

Paediatric CFS/ME is a severe debilitating illness causing significant levels of school absence. About a third of children with CFS/ME have high levels of anxiety. We wanted to find out what was known about treatment approaches for anxiety in children with CFS/ME and what is known about the impact of co-morbid anxiety on outcome in CFS/ME. Whilst CBT appears to result in lower levels of anxiety at follow up, there was insufficient evidence to conclude what the best treatment is for dealing with anxiety in paediatric CFS/ME patients.

Author's Contribution

ML conceived the study and designed the study protocol. SS, ML, NL, VR and AB did the data search and data synthesis. EC resolved conflicts. SS drafted the manuscript and ML and EC reviewed and edited the manuscript. All authors reviewed the paper before submission.

List of Figures:

Figure 1. Systematic review flow chart (based on PRISMA guidelines)[40]

List of Abbreviations

CDC: Centres for Disease Control and prevention

CBT: Cognitive Behaviour Therapy

CFS: Chronic Fatigue Syndrome

CIS-20: Checklist Individual Strength-20

DAWBA: Development And Well Being Assessment

GAD: Generalised Anxiety Disorder

GET: Graded Exercise Therapy

HADS: Hospital Anxiety and Depression Scale

MASC: Multidimensional Anxiety Scale for Children

ME: Myalgic Encephalomyelitis/Encephalopathy

NICE: National Institute for Health and Clinical Excellence

RCTs: Randomised Controlled Trials

STAIC: State-Trait Anxiety Inventory for Children

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Conflict of interest statement: Esther Crawley is a medical advisor for the Sussex & Kent ME/CFS Society. There are no other conflicts of interest.

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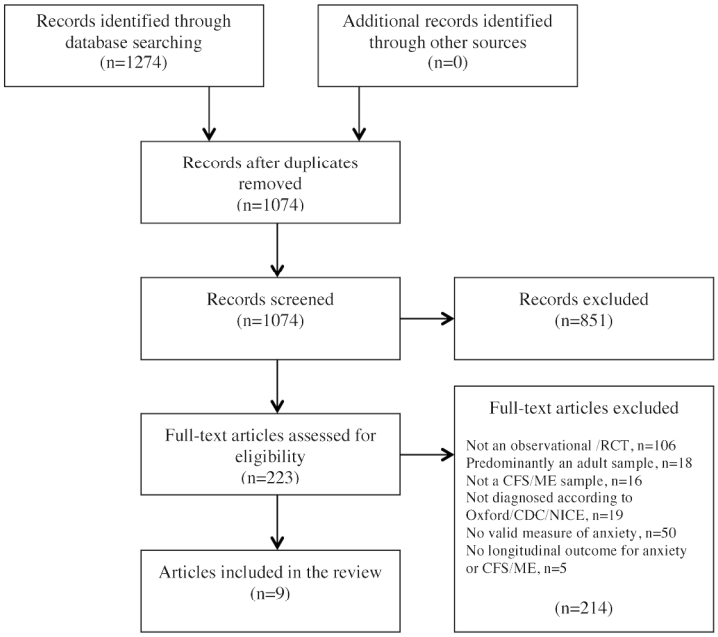

Figure 1. Systematic review flow chart (based on PRISMA guidelines)

179x232mm (600 x 600 DPI)

Supplementary Information

Search Terms used in OVID and Cochrane Library

Paediatric	CFS/ME
adolesc*.tw preadolesc*.tw pre-adolesc*.tw boy*.tw girl*.tw child*.tw infan*.tw preschool*.tw pre-school*.tw juvenil*.tw minor*.tw p?ediatri*.tw pubescen*.tw pre-pubescen*.tw prepubescen*.tw puberty.tw teen*.tw young*.tw youth*.tw school*.tw high-school*.tw highschool*tw sibling*.tw schoolchild*.tw school child*.tw children.tw exp Adolescent exp child, preschool exp infant exp minors exp pediatr/ic	Chronic Fatigue Syndrome.tw myalgic encephal*.tw chronic fatigue syndrome*.mp. exp Fatigue Syndrome, Chronic/ myalgic encephal*.mp.

Supplementary Information

Quality Assessment

(a) Observational Studies

Authors (year)	Did the study address a clearly focused issue? Was this the outcome of interest to this review?	Was the cohort recruited in an acceptable way?	Was the exposure accurately measured to minimise bias?	Was the outcome accurately measured to minimise bias?	Confounding factors?	Follow-up of subjects complete enough and long enough?	Overall Rating using Cochrane risk of bias scale (low/unclear/high)
Chalder et al (2002)	Yes, No.	Yes	Yes	Yes	Can't tell	Can't tell, yes	Unclear
Diaz-Caneja et al (2007)	Can't tell, No	Can't tell	Can't tell	Can't tell	Yes	Yes, no	High
Lloyd et al (2012); Rimes et al (2014)	Yes, No	Yes	Yes	Yes	Can't tell	Can't tell, yes	Unclear
Rimes et al(2007)	Yes, No	Yes	Yes	Yes	Can't tell	Can't tell, yes	Unclear
Van de Putte et al (2007)	Yes, No	Yes	Yes	Yes	Can't tell	Can't tell, yes	Unclear

(b) Randomised controlled trials

Authors (year)	Did the trial address a clearly focused issue? Was this the outcome of interest to this review?	Was the assignment of patients to treatments randomised?	Were patients, healthcare professionals and research staff blinded?	Were the groups similar at the start of the trial?	Aside from the experimental investigation, were the groups treated equally?	Were all of the patients who entered the trial properly accounted for at its conclusion?	Overall Rating using Cochrane risk of bias scale (low/unclear/high)
Nijhof et al (2012); Nijhof et al (2013)	Yes, no	Yes	No	Yes	Yes	Can't tell	Low
Rowe (1997)	Yes, no	Yes	Yes	Yes	Yes	Yes	Low
Wright et al (2005)	Yes. no	Yes	No	Yes	Yes	Can't tell	Low

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1 in title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 2 and 4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 4 and supplementary material
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 4/5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 4/5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 4/5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 4/5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 5 and Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 5 and Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 8-11 and Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 15
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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